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1638	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/890,782	MEMELINK ET AL.	
	Examiner	Art Unit	
	Cynthia Collins	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-48* is/are pending in the application.

4a) Of the above claim(s) *37-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-36 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0801*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group III, claims 25-36 and 48, drawn to SEQ ID NOS: 3 and 6, in the reply filed on January 21, 2005 is acknowledged.

The traversal is on the ground(s) that Applicants believe that the lack of unity determination fails to comply with the requirements of PCT Rules. Applicants submit that the special technical feature linking the alleged groups is a jasmonate responsive Ap2-domain plant transcription factor. However, applicants believe that the cited reference fails to disclose suggest jasmonate responsive Ap2-domain transcription factor as set forth claims. Since there no art of record that discloses the AP2-domain containing transcription factors as set forth the claims, is believed that the jasmonate responsive Ap2-domain plant transcription factors provide a contribution over the prior and thus constitute a special technical feature within the meaning PCT Rule 13.2.

This is not found persuasive because the induction of expression of an Ap2-domain plant transcription factor gene by jasmonate is not a technical feature of the Ap2-domain plant transcription factor protein. The induction of expression of an Ap2-domain plant transcription factor gene by jasmonate is a technical feature of the Ap2-domain plant transcription factor gene promoter. The inventions of Groups I-VI are not linked by Ap2-domain plant transcription factor gene promoters, or by jasmonate inducible promoters. The technical feature linking the inventions of Groups I-VI is AP2-domain containing transcription factor proteins and the polynucleotides that encode them, which proteins and coding sequences are known in the prior art, as set forth in the restriction requirement mailed October 21, 2004.

Claims 37-47 are withdrawn as being directed to nonelected inventions.

The requirement is still deemed proper and is therefore made FINAL.

Claim Objections

Claims 25 and 48 are objected to because the claims recite nonelected sequences. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-36 and 48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a nucleic acid molecule comprising a nucleotide sequence selected from: (a) SEQ ID NO: 3; (b) a nucleotide sequence encoding an Ap2-domain transcription factor that is involved in the response of a plant cell to a jasmonate; and (c) a nucleotide sequence encoding a variant of the Ap2-domain transcription factor comprising at least one Ap2-domain having an amino acid sequence with at least 40% homology to AP2-domain of SEQ ID NO:6, and to methods of using said nucleic acid molecule to transform cells.

The specification describes two nucleotide sequences obtained from *Catharanthus roseus* that encode AP2-domain transcription factors that comprise a single Ap2 domain and that are natively expressed in response to jasmonate treatment of *Catharanthus roseus* cells, SEQ ID NOS: 2 and 3 (pages 59-65). The specification does not describe variants of SEQ ID NO:3, or other nucleotide sequences obtained from other sources that encode AP2-domain transcription factors that comprise more than one Ap2 domain and that are otherwise involved in the response of plant cells to a jasmonate.

The Federal Circuit has recently clarified the application of the written description requirement. The court stated that "A description of a genus of cDNAs may be achieved by means of recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." See *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1569; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

In the instant case Applicant has not described a representative number of species falling within the scope of the claimed genus which encompasses numerous undisclosed and uncharacterized sequences obtained from any source that encode AP2-domain transcription factor variants that comprise one or more Ap2 domains and that are involved in any way in the response of plant cells to a jasmonate, nor the structural features unique to the genus.

Claims 25-36 and 48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleotide sequence encoding SEQ ID NO:6, for nucleotide sequences encoding the truncations of SEQ ID NO:6 that are disclosed as Δ5ORCA3

and Δ3ORCA3, and for methods of transforming *Catharanthus roseus* cells with said nucleotide sequences operably linked to a promoter in a sense orientation, does not reasonably provide enablement for nucleotide sequences encoding variants of SEQ ID NO:6, or for other methods of using nucleotide sequences encoding SEQ ID NO:6 or truncations or variants thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to a nucleic acid molecule comprising a nucleotide sequence selected from: (a) SEQ ID NO: 3; (b) a nucleotide sequence encoding an Ap2-domain transcription factor that is involved in the response of a plant cell to a jasmonate; and (c) a nucleotide sequence encoding a variant of the Ap2-domain transcription factor comprising at least one Ap2-domain having an amino acid sequence with at least 40% homology to AP2-domain of SEQ ID NO:6.

The claims are also drawn to methods of modulating in a cell the level(s) of one or more metabolites, including wherein the at least one metabolite is a plant metabolite, including but not limited to precursors and/or intermediates therefor wherein the plant metabolite is a secondary plant metabolite selected from the group consisting of alkaloid compounds, phenolic compounds or terpenoid compounds such as a terpenoid indole alkaloid, and/or of modulating the expression of one or more genes involved in the biosynthesis of a metabolite or a precursor therefor, including wherein the gene involved in the biosynthesis of the metabolite encodes a protein or polypeptide, including but not limited to an enzyme, said method comprising providing to the cell, including a plant cell, an Ap2-domain transcription factor that is involved in the response of

a plant cell to a jasmonate, or a variant of the Ap2-domain transcription factor comprising at least one Ap2-domain having an amino acid sequence with at least 40% amino acid identity with an AP2- domain of SEQ ID NO:6, including methods wherein the provision of the Ap2-domain transcription factor or variant thereof results in a modulation of the stress resistance of a cell, including methods wherein the Ap2-domain transcription factor or variant thereof is provided to the cell by the expression in said cell under the control of an expression regulating sequence operable in said cell, including an expression regulating sequence that is heterologous to the cell and/or an expression regulating sequence that is an expression regulating sequence with which the nucleotide sequence that encodes the Ap2-domain transcription factor or variant thereof is not natively associated, of a nucleotide sequence that encodes the Ap2-domain transcription factor or variant thereof.

The claims are additionally drawn to said methods where in the cell to which the Ap2-domain transcription factor or variant thereof has been provided: the level in the cell of at least one metabolite is enhanced by at least 10%, at least 25% or at least 100%, relative to a cell to which the transcription factor or variant thereof is not provided; and/or the level in the cell of the at least one metabolite 25% or at least is reduced by at least 10%, at least 50%, or at least 95%, relative to a cell to which the transcription factor or variant thereof is not provided.

The claims are further drawn to said methods where in the cell to which the Ap2-domain transcription factor or variant thereof has been provided: the expression in the cell of one or more genes involved in the biosynthesis of a metabolite or a precursor therefor is enhanced by at least 10%, at least 25% or at least 100%, relative to a cell to which the transcription factor is not provided; and/or the expression in the cell of one or more genes involved in the biosynthesis of a

metabolite or a precursor therefor is reduced by at least 10%, at least 25% or at least 50%, or at least 95%, relative to a cell to which the transcription factor is not provided.

The specification discloses the isolation of the elected nucleotide sequence of SEQ ID NO:3 from *Catharanthus roseus* , which sequence encodes an AP2-domain transcription factor of SEQ ID NO:6 (also designated ORCA-3) that comprises a single Ap2 domain and that is natively expressed in response to jasmonate treatment of *Catharanthus roseus* cells (pages 59-65).

The specification also discloses that ORCA-3 can transactivate the expression of a *gusA*-reporter gene operably linked to a *Tdc* or *Str1* promoter when an expression vector containing the *Orca-3* cDNA in the sense orientation in cotransformed into *Catharanthus roseus* cells (pages 68-69). The specification additionally discloses that ORCA-3 can transactivate the expression of a *gusA*-reporter gene operably linked to the jasmonate-responsive RV element of from the *Str1* promoter when an expression vector containing the *Orca-3* cDNA in the sense orientation is cotransformed into *Catharanthus roseus* cells (page 69).

The specification further discloses that deletion of the acidic region preceding the AP2 domain from ORCA-3 abolishes most of the ORCA-3 transactivation of the expression of a *gusA*-reporter gene operably linked to the *Str1* promoter when an expression vector containing the truncated *Orca-3* cDNA in the sense orientation (Δ5ORCA3) is cotransformed into *Catharanthus roseus* cells (page 71). The specification also discloses that deletion of the serine rich region C-terminal of the AP2 domain from ORCA-3 increases the ORCA-3 transactivation of the expression of a *gusA*-reporter gene operably linked to the *Str1* promoter when an

expression vector containing the truncated *Orca-3* cDNA in the sense orientation (Δ3ORCA3) is cotransformed into *Catharanthus roseus* cells (page 69).

The specification additionally discloses that native TIA terpenoid indole alkaloid (TIA) secondary metabolite biosynthetic genes *Tdc*, *Str*, *Cpr* and *D4h* are expressed at higher levels in *Catharanthus roseus* cells transformed with an expression vector containing the *Orca-3* cDNA operably linked to a 2B4A1 promoter in a sense orientation (O3-OX cells) , as are native *Asa* and *Dxs*, genes whose products produce TIA precursors, whereas the native TIA biosynthetic genes *Sgd* and *G10h* are not expressed at higher levels (page 72). The specification further discloses that levels of tryptophan and trytptamine are increased in O3-OX cells as compared to control cells, and that O3-OX cells do not accumulate alkaloids (page 73).

The specification does not disclose how to make nucleotide sequences encoding variants of the Ap2-domain transcription factor that comprise at least one Ap2-domain having an amino acid sequence with at least 40% homology to AP2-domain of SEQ ID NO:6 and that can be used to achieve the desired effects.

The specification does not disclose how to use ORCA-3 (SEQ ID NO:6) or variants thereof to modulate the level of metabolites other than tryptophan and trytptamine, or how to use ORCA-3 to modulate the level of metabolites tryptophan and trytptamine other than by increasing their levels.

The specification does not disclose how to use ORCA-3 or variants thereof to modulate the expression of genes other than *Tdc*, *Str*, *Cpr, D4h, Asa* and *Dxs*, or how to use ORCA-3 to modulate the expression of *Tdc*, *Str*, *Cpr, D4h, Asa* and *Dxs* other than by increasing their expression.

The specification does not disclose how to provide ORCA-3 (SEQ ID NO:6) to a cell other than by transforming cells with an expression vector containing the *Orca-3* cDNA (SEQ ID NO:3) operably linked to a promoter in a sense orientation, or how to achieve the desired results using cells other than *Catharanthus roseus* cells

The specification does not disclose how to use ORCA-3 or variants thereof to modulate in any way the resistance of a cell to any particular type of stress.

The specification does not disclose how to use ORCA-3 (SEQ ID NO:6) or variants thereof to enhance or reduce the specific % level of a metabolite. The specification does not disclose how to use ORCA-3 (SEQ ID NO:6) or variants thereof to enhance or reduce the specific % level of the expression of a gene.

The full scope of the claimed invention is not enabled because the effect of expressing nucleotide sequences encoding variants of the Ap2-domain transcription factor that comprise at least one Ap2-domain having an amino acid sequence with at least 40% homology to AP2-domain of SEQ ID NO:6 is unpredictable, as the functional effect of altering the amino acid sequence of an Ap2-domain transcription factor or altering the number Ap2-domains in an Ap2-domain transcription factor is unpredictable.

See, for example, Krizek B.A. (AINTEGUMENTA utilizes a mode of DNA recognition distinct from that used by proteins containing a single AP2 domain. Nucleic Acids Res. 2003 Apr 1;31(7):1859-68), who teaches that each AINTEGUMENTA AP2 domain uses different amino acids to contact the DNA consensus sequence for AINTEGUMENTA binding, and that amino acids in the linker region connecting the two AINTEGUMENTA AP 2 domains are also

important for AINTEGUMENTA function (abstract; page 1864; page 1865 Figure 4; pages 1866-1867).

In the instant case the specification does not provide sufficient guidance with respect to how to make nucleotide sequences encoding variants of the Ap2-domain transcription factor that comprise at least one Ap2-domain having an amino acid sequence with at least 40% homology to AP2-domain of SEQ ID NO:6 wherein the variants function as desired upon expression in a cell transformed therewith. Absent such guidance one skilled in the art would have design and test in cells transformed therewith the effect of expressing numerous variant sequences in order to determine which sequences encoding variants of the Ap2-domain transcription factor function as desired and which do not. Such a trial and error to practicing the claimed invention would constitute undue experimentation.

The full scope of the claimed invention is also not enabled because the effect of expressing SEQ ID NO:6 or variants thereof on the level of metabolites other than tryptophan and trytptamine is unpredictable, as SEQ ID NO:6 and variants thereof would require the presence of particular cis-acting sequences in the promoters of metabolite biosynthetic genes in order to mediate their effects, and not all metabolite biosynthetic genes would comprise the requisite cis-acting sequences in their promoters. Likewise, the effect of expressing SEQ ID NO:6 or variants thereof on the expression of genes other than *Tdc*, *Str*, *Cpr, D4h, Asa* and *Dxs* is unpredictable.

See, for example, Van der Fits L. et al. (ORCA3, a jasmonate-responsive transcriptional regulator of plant primary and secondary metabolism. Science. 2000 Jul 14;289(5477):295-7), who teach that terpenoid indole alkaloid (TIA) secondary metabolite biosynthetic genes *Tdc*, *Str*,

Cpr and *D4h* were induced by ORCA3 overexpression in transformed *Catharanthus roseus* cells, whereas two other TIA biosynthetic genes, *G10h* and *Dat*, were not induced by ORCA3 overexpression (paragraph spanning pages 295-296; page 296 Figure 3). Van der Fits L. et al. also teach that genes encoding the alpha subunit of AS(Asα) and DSX, enzymes involved in primary metabolism leading to TIA precursor synthesis were induced by ORCA3 overexpression, whereas two other primary metabolite genes not involved in the production of TIA precursors , *Ggpps* and *Ics*, were not induced by ORCA3 overexpression (paragraph spanning pages 295-296; page 296 Figure 3).

In the instant case the specification does not provide sufficient guidance with respect to how to use SEQ ID NO:6 or variants thereof to alter the level of metabolites other than tryptophan and trytptamine. The specification also does not provide sufficient guidance with respect to how to use SEQ ID NO:6 or variants thereof to alter the expression of genes other than *Tdc*, *Str*, *Cpr, D4h, Asa* and *Dxs*. Absent such guidance one skilled in the art would have evaluate the effect of SEQ ID NO:6 on the level of numerous different metabolites, and on the expression of numerous different genes, in order to determine which metabolites and genes would be affected by SEQ ID NO:6 or variants thereof and which would not. Such a trial and error to practicing the claimed invention would constitute undue experimentation.

The full scope of the claimed invention is additionally not enabled because methods of using sequences encoding SEQ ID NO:6 or variants thereof to modulate the level of metabolites tryptophan and trytptamine other than by increasing their levels are unpredictable, as methods that would produce an effect opposite of that produced by sense expression of a sequence encoding SEQ ID NO:6, such as antisense methods, are unpredictable. Likewise methods of

using SEQ ID NO:6 or variants thereof to modulate the expression of *Tdc*, *Str*, *Cpr*, *D4h*, *Asa* and *Dxs* other than by increasing their expression are unpredictable.

See, for example, Sandler S.J. et al. (Inhibition of gene expression in transformed plants by antisense RNA. Plant Molecular Biology, 1988, Vol. 11, No. 3, pages 301-310), who teach that DNA fragments encoding different portions of the nopaline synthase gene, when expressed as antisense transcripts, vary in their ability to inhibit nopaline synthase gene expression (page 308 column 2 and Table 4, page 309 column 1 first full paragraph). Antisense transcripts downstream from the Cla I site (nucleotide 373) effectively suppressed nopaline synthase gene expression, whereas the full length antisense transcript and the antisense transcript upstream from the Cla I site (nucleotides 1 to 373) did not (id).

See also, for example, van der Krol A.R. et al. (Inhibition of flower pigmentation by antisense CHS genes: promoter and minimal sequence requirements for the antisense effect. Plant Mol Biol. 1990 Apr;14(4):457-66), who teach a method of decreasing the expression of an endogenous petunia chalcone synthase gene by transforming petunia cells with chimeric genes comprising chalcone synthase (CHS) coding sequences operably linked in an antisense orientation to a CaMV 35S constitutive promoter. The full length CHS cDNA and CHS sequences encoding half-length or quarter-length RNA complementary to the 3' half of the CHS mRNA decreased the expression of endogenous CHS, whereas half-length RNA complementary to the 5' half of the CHS mRNA did not (page 460 Figures 1 and 2;page 461 Figure 3).

See additionally, for example, Waterhouse et al. (Virus resistance and gene silencing: killing the messenger. Trends Plant Sci. 1999 Nov;4(11):452-457), who teach that antisense suppression of gene expression requires a high degree of sequence homology (>75%) between

the endogenous sequence and the antisense transgene to be effective (page 453 column 1 second full paragraph).

In the instant case the specification does not provide sufficient guidance with respect to how to use SEQ ID NO:6 or variants thereof to produce an effect opposite of that produced by sense expression of a sequence encoding SEQ ID NO:6. Absent such guidance one skilled in the art would have evaluate the effect of different types of methodologies that utilize SEQ ID NO:6 or variants thereof on the levels of tryptophan and trytptamine and on the levels of the expression of *Tdc*, *Str*, *Cpr*, *D4h*, *Asa* and *Dxs* in order to identify and optimize a methodology that that would produce an effect opposite of that produced by sense expression of a sequence encoding SEQ ID NO:6. Such a trial and error to practicing the claimed invention would constitute undue experimentation.

The full scope of the claimed invention is further not enabled because methods for providing SEQ ID NO:6 or variants thereof to a cell other than by transforming cells with an expression vector containing a sequence encoding SEQ ID NO:6 operably linked to a promoter in a sense orientation, as the employment of other methods may be affected by numerous variables including but not limited to protein stability and the physiological state of the cell.

See for example McElligott M.A. et al. (Lysosomal degradation of ribonuclease A and ribonuclease S-protein microinjected into the cytosol of human fibroblasts. J Biol Chem. 1985 Oct 5;260(22):11986-93), who teach that purified ribonuclease A and ribonuclease S are subject to lysosomal degradation upon microinjection into human lung fibroblast cells, which degradation is affected by the presence or absence of serum and ammonium chloride (page 11986 abstract; page 11989 Figures 3-5; page 11990 Table I). McElligott et al. also teach that

bovine serum albumin is subject to cytosolic degradation upon microinjection into human lung fibroblast cells (page 11990 Figure 6; page 11991 Table II). McElligott et al. additionally teach that 60% of rat liver cytosolic proteins are subject to cytosolic degradation and 40% of rat liver cytosolic proteins are subject to lysosomal degradation upon microinjection into human lung fibroblast cells (page 11991 Table II). McElligott et al. further teach that the relative importance of lysosomal and non-lysosomal pathways of protein degradation may vary with cell type and physiological conditions (page 11986 column 1 third full paragraph). See also for example Estelle M. (Proteases and cellular regulation in plants. Curr Opin Plant Biol. 2001 Jun;4(3):254-60. Review), who teaches that protein stability and proteolysis in plant cells is likewise variable.

In the instant case the specification does not provide sufficient guidance with respect to how to use other methods to provide cells with SEQ ID NO:6 or variants thereof in a manner that would result in the desired effect. Absent such guidance one skilled in the art would have evaluate the effectiveness of different types of methodologies for providing SEQ ID NO:6 or variants to cells in order to identify and optimize a methodology that that would result in the desired effect. Such a trial and error to practicing the claimed invention would constitute undue experimentation.

The full scope of the claimed invention is also not enabled because the desired results cannot predictably be achieved using cells other than *Catharanthus roseus* cells, as other types of cells may or may not comprise the appropriate native genes having requisite cis-acting sequences for SEQ ID NO:6 in their promoters.

See, for example, Memelink J. et al. (ORCAnization of jasmonate-responsive gene expression in alkaloid metabolism. Trends Plant Sci. 2001 May;6(5):212-9. Review), who teach

that most classes of secondary metabolites are found only in specific plant families or genera, and each plant species contains a distinct profile of secondary metabolites which establishes a unique metabolic fingerprint, and that about 20% of plant species accumulate alkaloids (page 212 column 1).

See also, for example, Riechmann J.L. et al. (The AP2/EREBP family of plant transcription factors. Biol Chem. 1998 Jun;379(6):633-46. Review), who teach that the AP2/EREBP family of plant transcription factors is unique to plants (page 633 abstract and column 2 first paragraph).

In the instant case the specification does not provide sufficient guidance with respect to which cell types comprise the appropriate native genes having requisite cis-acting sequences in their promoters such that the desired results can be achieved upon expression in the cells of SEQ ID NO:6 or its variants. Absent such guidance one skilled in the art would have test the effect of expressing SEQ ID NO:6 or its variants on a variety of different cell types in order to determine which cell types comprise the appropriate native genes having requisite cis-acting sequences in their promoters and which do not. Such a trial and error to practicing the claimed invention would constitute undue experimentation.

The full scope of the claimed invention is additionally not enabled because the effect of SEQ ID NO:6 or variants thereof on the resistance of a cell to any particular type of stress is unpredictable, as the resistance of a cell to a particular type of stress requires the presence of a variety of different types of gene products produced by native genes which genes may or may not have the requisite cis-acting sequences for SEQ ID NO:6 in their promoters.

See, for example, Liu Q. et al. (Two transcription factors, DREB1 and DREB2, with an EREBP/AP2 DNA binding domain separate two cellular signal transduction pathways in drought- and low-temperature-responsive gene expression, respectively, in *Arabidopsis*. Plant Cell. 1998 Aug;10(8):1391-406), who teach that two transcription factors, DREB1 and DREB2, function in two separate signal transduction pathways under low temperature and dehydration conditions respectively. The expression of DREB1 transcription factors is induced by low-temperature stress, whereas the expression of DREB2 transcription factors is induced by dehydration and high-salt stress (page 1398 Figure 6). Furthermore, overexpression of DREB1 in transgenic plants induced the expression of rd29A, a gene whose expression is induced by dehydration, high salt and low temperature stress in nontransgenic wild type plants, whereas overexpression of DREB2 did not induce rd29A expression (page 1402 Figure 11).

In the instant case the specification does not provide sufficient guidance with respect to how to use SEQ ID NO:6 or variants thereof to increase the resistance of a cell to a particular type of stress. Absent such guidance one skilled in the art would have test the effect of expressing SEQ ID NO:6 or its variants on the resistance of a cell to a variety of different types of stresses in order to determine which type of stress resistance, if any, would be increased in a cell. Such a trial and error to practicing the claimed invention would constitute undue experimentation.

The full scope of the claimed invention is further not enabled because the extent to which SEQ ID NO:6 or variants thereof could enhance or reduce the specific % level of a metabolite or the specific % level of the expression of a gene is unpredictable, as such specific effects are known to be variable and depend on a number of factors including but not limited to the level of

expression of SEQ ID NO:6 or variants thereof, the maximum rate of gene expression in the presence of saturating levels of SEQ ID NO:6 or variants thereof, the stability of gene products expressed, the availability of substrates for the gene products to act on, and the stability of the metabolites produced.

See, for example, Park J.M. et al. (Overexpression of the tobacco Tsi1 gene encoding an EREBP/AP2-type transcription factor enhances resistance against pathogen attack and osmotic stress in tobacco. Plant Cell. 2001 May;13(5):1035-46), who teach that overexpression of the tobacco Tsi1 gene encoding an EREBP/AP2-type transcription factor in tobacco cells induced at varying levels the expression of several pathogenesis-related genes under normal conditions (page 1041 Figure 7).

In the instant case the specification does not provide sufficient guidance with respect to how to use SEQ ID NO:6 or variants thereof to enhance or reduce the specific % level of a metabolite or the specific % level of the expression of a gene. Absent such guidance one skilled in the art would have test the effect of expressing SEQ ID NO:6 or its variants on the specific % level of a metabolite or the specific % level of the expression of a gene in order to determine which metabolites or genes, if any, would be enhanced or reduced within the claimed parameters. Such a trial and error to practicing the claimed invention would constitute undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 25, and claims 26-36 dependent thereon, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 25 is indefinite in the recitation of "involved in the biosynthesis of a metabolite or a precursor therefor". It is unclear how the genes are "involved in" the biosynthesis of a metabolite or a precursor therefor, as a gene may be involved in the biosynthesis of a metabolite or a precursor therefor in more than one way (e.g. by encoding biosynthetic enzymes, by encoding proteins that regulate biosynthetic enzymes, etc.), and the nature of the involvement cannot be discerned from the elements recited in the claim.

Claims 25 and 48, and claims 26-36 dependent thereon, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 25 and 48 are indefinite in the recitation of "involved in the response of a plant cell to a jasmonate". It is unclear how the AP2-domain transcription factor is "involved in" the response of a plant cell to a jasmonate, as a transcription factor may be involved in the response of a plant cell to a jasmonate in more than one way (e.g. as a marker for the response of a plant cell to a jasmonate, as an effector for the response of a plant cell to a jasmonate, etc.), and the nature of the involvement cannot be discerned from the elements recited in the claims.

Claims 25 and 48, and claims 26-36 dependent thereon, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 25 and 48 are indefinite in the recitation of "an AP2-domain of SEQ ID NO:6". It is unclear what constitutes an AP2- domain

of SEQ ID NO:6, as neither the claims nor the specification define the identity and location of the amino acids of SEQ ID NO:6 that Applicants consider to constitute an AP2-domain.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 48 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claim 48 as written, does not sufficiently distinguish over nucleic acids as they exist naturally because the claim does not particularly point out any non-naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See Diamond v. Chakrabarty, 447 U.S. 303, 206 USPQ 193 (1980). The claim should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified", as taught by pages 63-64 of the specification. See MPEP 2105.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claim 48 is rejected under 35 U.S.C. 102(b) as being anticipated by M. Ohme-Takagi (*Nicotiana tabacum* mRNA for ERF1, complete CDS, EMBL Accession No. D3823, 01 May 1995, Applicant's IDS).

The claim is drawn to a nucleic acid molecule comprising a nucleotide sequence encoding a variant of the Ap2-domain transcription factor comprising at least one Ap2-domain having an amino acid sequence with at least 40% homology to AP2-domain of SEQ ID NO:6.

M. Ohme-Takagi teach a nucleic acid molecule comprising a nucleotide sequence encoding a variant of the Ap2-domain transcription factor comprising at least one Ap2-domain having an amino acid sequence with at least 40% homology to AP2-domain of SEQ ID NO:6 (see attached alignment of SEQ ID NO:6 and M. Ohme-Takagi, TrEMBL Accession No. Q40476, 01 November 1996, *Nicotiana tabacum* ERF1 amino acid sequence).

Claims 25-36 and 48 are rejected under 35 U.S.C. 102(e) as being anticipated by Martin et al. (US Patent No. 6,653,533, issued November 25, 2003, filed June 14, 1999, claiming the

benefit of U.S. Provisional Application No. 60/019,633, filed Jun. 12, 1996 and U.S. Provisional Application No. 60/046,494, filed May 14, 1997).

The claims are drawn to a nucleic acid molecule comprising a nucleotide sequence encoding a variant of the Ap2-domain transcription factor comprising at least one Ap2-domain having an amino acid sequence with at least 40% homology to AP2-domain of SEQ ID NO:6.

The claims are also drawn to methods of modulating in a cell the level(s) of one or more metabolites, including wherein the at least one metabolite is a plant metabolite, including but not limited to precursors and/or intermediates therefor wherein the plant metabolite is a secondary plant metabolite selected from the group consisting of alkaloid compounds, phenolic compounds or terpenoid compounds such as a terpenoid indole alkaloid, and/or of modulating the expression of one or more genes involved in the biosynthesis of a metabolite or a precursor therefor, including wherein the gene involved in the biosynthesis of the metabolite encodes a protein or polypeptide, including but not limited to an enzyme, said method comprising providing to the cell, including a plant cell, an Ap2-domain transcription factor that is involved in the response of a plant cell to a jasmonate, or a variant of the Ap2-domain transcription factor comprising at least one Ap2-domain having an amino acid sequence with at least 40% amino acid identity with an AP2- domain of SEQ ID NO:6, including methods wherein the provision of the Ap2-domain transcription factor or variant thereof results in a modulation of the stress resistance of a cell, including methods wherein the Ap2-domain transcription factor or variant thereof is provided to the cell by the expression in said cell under the control of an expression regulating sequence operable in said cell, including an expression regulating sequence that is heterologous to the cell and/or an expression regulating sequence that is an expression regulating sequence with which

the nucleotide sequence that encodes the Ap2-domain transcription factor or variant thereof is not natively associated, of a nucleotide sequence that encodes the Ap2-domain transcription factor or variant thereof.

The claims are additionally drawn to said methods where in the cell to which the Ap2-domain transcription factor or variant thereof has been provided: the level in the cell of at least one metabolite is enhanced by at least 10%, at least 25% or at least 100%, relative to a cell to which the transcription factor or variant thereof is not provided; and/or the level in the cell of the at least one metabolite 25% or at least is reduced by at least 10%, at least 50%, or at least 95%, relative to a cell to which the transcription factor or variant thereof is not provided.

The claims are further drawn to said methods where in the cell to which the Ap2-domain transcription factor or variant thereof has been provided: the expression in the cell of one or more genes involved in the biosynthesis of a metabolite or a precursor therefor is enhanced by at least 10%, at least 25% or at least 100%, relative to a cell to which the transcription factor is not provided; and/or the expression in the cell of one or more genes involved in the biosynthesis of a metabolite or a precursor therefor is reduced by at least 10%, at least 25% or at least 50%, or at least 95%, relative to a cell to which the transcription factor is not provided.

Martin et al. teach a nucleic acid molecule comprising a nucleotide sequence encoding a variant of the Ap2-domain transcription factor comprising at least one Ap2-domain having an amino acid sequence with at least 40% homology to AP2-domain of SEQ ID NO:6 (see attached alignments of SEQ ID NO:6 and US Patent No. 6,653,533 SEQ ID NOS: 1 and 2).

Martin et al. also teach a method comprising providing to a plant cell said variant of the Ap2-domain transcription factor wherein the variant results in a modulation of the pathogen

stress resistance of the plant cell, wherein the variant is provided to the cell by the expression in said cell under the control of a heterologous expression regulating sequence operable in said cell (column 8 line 59 through column 9 line 16; columns 34-36).

While Martin et al. are silent with respect to whether their method modulates in a cell the level(s) of one or more metabolites, including wherein the at least one metabolite is a plant metabolite, including but not limited to precursors and/or intermediates therefor wherein the plant metabolite is a secondary plant metabolite selected from the group consisting of alkaloid compounds, phenolic compounds or terpenoid compounds such as a terpenoid indole alkaloid, and/or of modulating the expression of one or more genes involved in the biosynthesis of a metabolite or a precursor therefor, including wherein the gene involved in the biosynthesis of the metabolite encodes a protein or polypeptide, including but not limited to an enzyme, Martin et al. need not explicitly teach this limitation to anticipate the claimed invention, as this limitation is an intended use that does not limit the claimed method.

While Martin et al. are silent with respect to the extent to which the level in the cell of at least one metabolite is enhanced or reduced, Martin et al. need not explicitly teach this limitation to anticipate the claimed invention, as this limitation is an inherent consequence of expressing the variant protein.

While Martin et al. are silent with respect to the extent to which the expression in the cell of one or more genes involved in the biosynthesis of a metabolite or a precursor therefor is enhanced or reduced, Martin et al. need not explicitly teach this limitation to anticipate the claimed invention, as this limitation is an inherent consequence of expressing the variant protein.

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia Collins whose telephone number is (571) 272-0794. The examiner can normally be reached on Monday-Friday 8:45 AM -5:15 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Cynthia Collins
Examiner
Art Unit 1638

CC

Cynthia Collins 4/15/05